

FILE 'HOME' ENTERED AT 18:31:22 ON 02 DEC 1999

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.60	0.60

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STRUCTURE FILE UPDATES: 01 DEC 99 HIGHEST RN 249649-97-6
DICTIONARY FILE UPDATES: 01 DEC 99 HIGHEST RN 249649-97-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

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POTENTIAL STEREO BOND SEARCH PROBLEM WITH STN EXPRESS WITH DISCOVER!
5.0 (Windows Only) SEE NEWS 9 FOR DETAILS

=> s gatggagggcgccatggcggg/sqsn

L1 249 GATGGAGGGCGGCATGGCGGG/SQSN

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	24.20	24.80

FILE 'CAPLUS' ENTERED AT 18:36:24 ON 02 DEC 1999
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FILE COVERS 1967 - 2 Dec 1999 VOL 131 ISS 23
FILE LAST UPDATED: 1 Dec 1999 (19991201/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

This file supports REGISTRY for direct browsing and searching of
all substance data from the REGISTRY file. Enter HELP FIRST for
more information.

=> s l1 and adenosine

5 L1
55296 ADENOSINE

584 ADENOSINES
55424 ADENOSINE
(ADENOSINE OR ADENOSINES)

L2 5 L1 AND ADENOSINE

=> d fhitrstr ibib abs 1-5

L2 ANSWER 1 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT 186470-20-2

RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine A1 receptor-specific; antisense oligonucleotides
capable of binding to multiple targets and their use in treatment of
respiratory disease)

RN 186470-20-2 CAPLUS

CN DNA, d(P-thio)(G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA
INDEX

NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1999:219995 CAPLUS

DOCUMENT NUMBER: 130:306599

TITLE: Antisense oligonucleotides capable of binding to
multiple targets and their use in the treatment of
respiratory disease

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913886	A1	19990325	WO 1998-US19419	19980917
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893951	A1	19990405	AU 1998-93951	19980917
PRIORITY APPLN. INFO.:			US 1997-59160	19970917
			US 1998-93972	19980609
			WO 1998-US19419	19980917

AB Antisense oligonucleotides carrying sequences that will allow them to
bind

to more than one mRNA in a target cell are described. Such
oligonucleotides can be used as a single treatment for diseases having
more than one contributing pathway. In particular, oligonucleotides
effective against genes involved in the etiol. of respiratory disease are
targeted. Preferably, the oligonucleotides are low in adenosine
(.ltoreq.15%) and may have adenosines substituted with analogs.
These oligonucleotides are targeted to high (G+C) sequences within mRNAs.

Thus, phosphorothioate antisense oligonucleotide (HAdAlAS, 5'-gatggagggcgcatggcggg-3') designed for the **adenosine** A1 receptor is provided. HAdAlAS significantly and specifically reduces the in vivo response to **adenosine** challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 **adenosine** and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition assocd. with lung airway, such as bronchoconstriction, inflammation, or allergies.

L2 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT 208884-01-9

RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use);
BIOL (Biological study); PROC (Process); USES (Uses)
(nucleotide sequence; antisense oligonucleotides for treatment of
respiratory ailments and lung inflammation)

RN 208884-01-9 CAPLUS

CN DNA (synthetic human adenosine A1 receptor mRNA-binding cDNA) (9CI) (CA
INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1998:385522 CAPLUS

DOCUMENT NUMBER: 129:72195

TITLE: Agent and method of treatment for diseases and
conditions associated with respiratory ailments and
lung inflammation

INVENTOR(S): Nyce, Jonathan W. ✓

PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9823294	A1	19980604	WO 1997-US22017	19971126
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9853688	A1	19980622	AU 1998-53688	19971126
EP 946201	A1	19991006	EP 1997-950775	19971126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			US 1996-757024	19961126
			WO 1997-US22017	19971126

AB An agent comprises anti-sense oligos directed to **adenosine** receptors for alleviation of respiratory ailments and inflammation. The agent is provided as a compn., various formulations, and kit. The present agents may be administered in an anti-bronchoconstriction and/or

anti-inflammation effective amt. to alleviate the bronchoconstriction and inflammation afflicting a subject. Preferred agents contain anti-sense oligonucleotide targeting the **adenosine** A1, A2a, A2b and/or A3 receptors and bradykinin B2 receptor. The method is useful for treating patients afflicted with asthma and other respiratory problems. Pharmaceutical formulations are also disclosed.

L2 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT **188704-72-5**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA antisense therapy for asthma in animal model)

RN 188704-72-5 CAPLUS

CN DNA, d(G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1997:145753 CAPLUS

DOCUMENT NUMBER: 126:246517

TITLE: DNA antisense therapy for asthma in an animal model

AUTHOR(S): Nyce, Jonathan W.; Metzger, W. James

CORPORATE SOURCE: Dep. Molecular Pharmacology, EpiGenesis Pharmaceuticals, Greenville, NC, 27834, USA

SOURCE: Nature (London) (1997) 385(6618), 721-725

CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Macmillan Magazines

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Asthma is an inflammatory disease characterized by bronchial hyper-responsiveness that can proceed to life-threatening airway obstruction. It is one of the most common diseases in industrialized countries, and in the United States accounts for about 1% of all health care costs. Asthma prevalence and mortality have increased dramatically over the past decade, and occupational asthma is predicted to be the pre-eminent occupational lung disease in the next decade. Increasing evidence suggests that **adenosine**, an endogenous purine that is involved in normal physiol. processes, may be an important mediator of bronchial asthma. In contrast to normal individuals, asthmatic individuals respond to **adenosine** challenge with marked airway obstruction, and concns. of **adenosine** are elevated in the bronchoalveolar lavage fluid of asthma patients. We performed a randomized crossover study using the dust mite-conditioned allergic rabbit

model of human asthma. Administration of an aerosolized phosphorothioate antisense oligodeoxynucleotide targeting the **adenosine** A1 receptor desensitized the animals to subsequent challenge with either **adenosine** or dust-mite allergen.

L2 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT **186470-20-2P**

RL: BAC (Biological activity or effector, except adverse); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)

(method of treatment for lung diseases using antisense oligonucleotides)

RN 186470-20-2 CAPLUS

CN DNA, d(P-thio)(G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1997:145207 CAPLUS

DOCUMENT NUMBER: 126:148487

TITLE: Method of treatment for lung diseases using antisense oligonucleotides

INVENTOR(S): Nyce, Jonathan W.; Metzger, W. James

PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.; Metzger, W. James

SOURCE: PCT Int. Appl., 71PP

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640162	A1	19961219	WO 1996-US9306	19960606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5994315	A	19991130	US 1995-474497	19950607
CA 2223776	AA	19961219	CA 1996-2223776	19960606
AU 9660959	A1	19961230	AU 1996-60959	19960606
EP 831848	A1	19980401	EP 1996-918260	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192686	A	19980909	CN 1996-196115	19960606
JP 11507218	T2	19990629	JP 1996-501658	19960606
PRIORITY APPLN. INFO.:			US 1995-474497	19950607
			WO 1996-US9306	19960606

AB A method of treating airway disease in a subject in need of such treatment

is disclosed. The method comprises topically administering to the subject

an antisense oligonucleotide in an amt. effective to treat the airway disease, where the antisense oligonucleotide is essentially free of adenosine. Pharmaceutical formulations are also disclosed.

L2 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT 186470-20-2P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(antisense oligonucleotides directed against adenosine A1 or A3 receptors for treatment of asthma)

RN 186470-20-2 CAPLUS

CN DNA, d(P-thio) (G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA INDEX

NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1997:130067 CAPLUS

DOCUMENT NUMBER: 126:135600
 TITLE: Antisense oligonucleotides directed against
adenosine A1 or A3 receptors for treatment of
 asthma
 INVENTOR(S): Nyce, Jonathan W.
 PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

1st

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO <u>9640266</u>	A1	19961219	WO 1996-US8325	19960603
W: AL, AM, AT, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2223769	AA	19961219	CA 1996-2223769	19960603
AU 9660295	A1	19961230	AU 1996-60295	19960603
AU 699330	B2	19981203		
EP 831924	A1	19980401	EP 1996-917910	19960603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192158	A	19980902	CN 1996-195955	19960603
AU 9918574	A1	19990506	AU 1999-18574	19990303
PRIORITY APPLN. INFO.:				
			US 1995-472527	19950607
			AU 1996-60295	19960603
			WO 1996-US8325	19960603

AB A method of reducing bronchoconstriction in a subject in need of such treatment is disclosed. The method comprises administering to the subject an antisense oligonucleotide mol. directed against the A1 or A3 **adenosine** receptor in an amt. effective to reduce bronchoconstriction. The method is useful for treating patients afflicted with asthma. Pharmaceutical formulations are also disclosed.

=> d fhitr 1-5

L2 ANSWER 1 OF 5 CAPLUS COPYRIGHT 1999 ACS

IT 186470-20-2

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**adenosine** A1 receptor-specific; antisense oligonucleotides capable of binding to multiple targets and their use in treatment of respiratory disease)

RN 186470-20-2 CAPLUS

CN DNA, d(P-thio) (G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L2 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1999 ACS
 IT **208884-01-9**
 RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use);
 BIOL (Biological study); PROC (Process); USES (Uses)
 (nucleotide sequence; antisense oligonucleotides for treatment of
 respiratory ailments and lung inflammation)
 RN 208884-01-9 CAPLUS
 CN DNA (synthetic human adenosine A1 receptor mRNA-binding cDNA) (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L2 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1999 ACS
 IT **188704-72-5**
 RL: BAC (Biological activity or effector, except adverse); THU
 (Therapeutic use); BIOL (Biological study); USES (Uses)
 (DNA antisense therapy for asthma in animal model)
 RN 188704-72-5 CAPLUS
 CN DNA, d(G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L2 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1999 ACS
 IT **186470-20-2P**
 RL: BAC (Biological activity or effector, except adverse); PNU
 (Preparation, unclassified); PRP (Properties); THU (Therapeutic use);
 BIOL
 (Biological study); PREP (Preparation); USES (Uses)
 (method of treatment for lung diseases using antisense
 oligonucleotides)
 RN 186470-20-2 CAPLUS
 CN DNA, d(P-thio) (G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA
 INDEX
 NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L2 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1999 ACS
 IT **186470-20-2P**
 RL: BAC (Biological activity or effector, except adverse); BPR
 (Biological
 process); PNU (Preparation, unclassified); PRP (Properties); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC
 (Process); USES (Uses)
 (antisense oligonucleotides directed against **adenosine** A1 or
 A3 receptors for treatment of asthma)
 RN 186470-20-2 CAPLUS
 CN DNA, d(P-thio) (G-A-T-G-G-A-G-G-G-C-G-G-C-A-T-G-G-C-G-G-G) (9CI) (CA
 INDEX
 NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d cost

COST IN U.S. DOLLARS

SINCE FILE TOTAL
 ENTRY SESSION

CONNECT CHARGES	0.90	2.70
SEARCH CHARGES	1.33	24.33
DISPLAY CHARGES	12.25	12.25

	14.48	39.28
CAPLUS FEE (5%)	0.72	0.72

FULL ESTIMATED COST	15.20	40.00
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-2.68	-2.68

IN FILE 'CAPLUS' AT 18:38:18 ON 02 DEC 1999

=> file registry

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	15.52	40.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-2.68	-2.68

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STRUCTURE FILE UPDATES: 01 DEC 99 HIGHEST RN 249649-97-6
 DICTIONARY FILE UPDATES: 01 DEC 99 HIGHEST RN 249649-97-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when
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POTENTIAL STEREO BOND SEARCH PROBLEM WITH STN EXPRESS WITH DISCOVER!
 5.0 (Windows Only) SEE NEWS 9 FOR DETAILS

=> s gttgttgggcatcttgcc/sqsn

L3 4 GTTGTGCGCATCTTGCC/SQSN

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	23.60	63.92

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-2.68

FILE 'CAPLUS' ENTERED AT 18:39:34 ON 02 DEC 1999
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FILE COVERS 1967 - 2 Dec 1999 VOL 131 ISS 23
FILE LAST UPDATED: 1 Dec 1999 (19991201/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> s l3 and antisense

3 L3
14550 ANTISENSE
18 ANTISENSES
14551 ANTISENSE
(ANTISENSE OR ANTISENSES)
L4 3 L3 AND ANTISENSE

=> d fhitstr 1-3

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 1999 ACS
IT **186470-21-3**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine A3 receptor-specific; **antisense** oligonucleotides capable of binding to multiple targets and their use in treatment of respiratory disease)
RN 186470-21-3 CAPLUS
CN DNA, d(P-thio)(G-T-T-G-T-T-G-G-G-C-A-T-C-T-T-G-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS
IT **186470-21-3P**
RL: PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treatment for lung diseases using **antisense** oligonucleotides)
RN 186470-21-3 CAPLUS
CN DNA, d(P-thio)(G-T-T-G-T-T-G-G-G-C-A-T-C-T-T-G-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS
IT **186470-21-3P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); PNU (Preparation, unclassified); PRP (Properties); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC
(Process); USES (Uses)

(**antisense** oligonucleotides directed against adenosine A1 or
A3 receptors for treatment of asthma)

RN 186470-21-3 CAPLUS

CN DNA, d(P-thio)(G-T-T-G-T-T-G-G-G-C-A-T-C-T-T-G-C-C) (9CI) (CA INDEX
NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d ibib abs 1-3

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:219995 CAPLUS

DOCUMENT NUMBER: 130:306599

TITLE: **Antisense** oligonucleotides capable of
binding to multiple targets and their use in the
treatment of respiratory disease

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913886	A1	19990325	WO 1998-US19419	19980917
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9893951	A1	19990405	AU 1998-93951	19980917
PRIORITY APPLN. INFO.:			US 1997-59160	19970917
			US 1998-93972	19980609
			WO 1998-US19419	19980917

AB **Antisense** oligonucleotides carrying sequences that will allow them to bind to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single treatment for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.ltoreq.15%) and may have adenosines substituted with analogs. These oligonucleotides are targeted to high (G+C) sequences within mRNAs.

Thus,
phosphorothioate **antisense** oligonucleotide (HAdA1AS, 5'-gatggagggcgcatggcggg-3') designed for the adenosine A1 receptor is provided. HAdA1AS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective

in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, or allergies.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS
 ACCESSION NUMBER: 1997:145207 CAPLUS
 DOCUMENT NUMBER: 126:148487
 TITLE: Method of treatment for lung diseases using
antisense oligonucleotides
 INVENTOR(S): Nyce, Jonathan W.; Metzger, W. James
 PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.;
 Metzger, W. James
 SOURCE: PCT Int. Appl., 71PP
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

#3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640162	A1	19961219	WO 1996-US9306	19960606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5994315	A	19991130	US 1995-474497	19950607
CA 2223776	AA	19961219	CA 1996-2223776	19960606
AU 9660959	A1	19961230	AU 1996-60959	19960606
EP 831848	A1	19980401	EP 1996-918260	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192686	A	19980909	CN 1996-196115	19960606
JP 11507218	T2	19990629	JP 1996-501658	19960606
PRIORITY APPLN. INFO.: US 1995-474497 19950607				
WO 1996-US9306 19960606				

AB A method of treating airway disease in a subject in need of such treatment is disclosed. The method comprises topically administering to the subject an **antisense** oligonucleotide in an amount effective to treat the airway disease, where the **antisense** oligonucleotide is essentially free of adenosine. Pharmaceutical formulations are also disclosed.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS
 ACCESSION NUMBER: 1997:130067 CAPLUS
 DOCUMENT NUMBER: 126:135600
 TITLE: **Antisense** oligonucleotides directed against adenosine A1 or A3 receptors for treatment of asthma
 INVENTOR(S): Nyce, Jonathan W.
 PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.
 SOURCE: PCT Int. Appl., 34 pp.

CODEN: PIXXD2
DOCUMENT TYPE: . Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640266	A1	19961219	WO 1996-US8325	19960603
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2223769	AA	19961219	CA 1996-2223769	19960603
AU 9660295	A1	19961230	AU 1996-60295	19960603
AU 699330	B2	19981203		
EP 831924	A1	19980401	EP 1996-917910	19960603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192158	A	19980902	CN 1996-195955	19960603
AU 9918574	A1	19990506	AU 1999-18574	19990303
PRIORITY APPLN. INFO.:				
				US 1995-472527 19950607
				AU 1996-60295 19960603
				WO 1996-US8325 19960603

AB A method of reducing bronchoconstriction in a subject in need of such treatment is disclosed. The method comprises administering to the subject

an **antisense** oligonucleotide mol. directed against the A1 or A3 adenosine receptor in an amt. effective to reduce bronchoconstriction. The method is useful for treating patients afflicted with asthma. Pharmaceutical formulations are also disclosed.

=> s gtgggcctagctctcgcc/sqsn

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L6 3 L5

=> d fhitr 1-3

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 1999 ACS

IT 186470-22-4

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adenosine A3 receptor-specific; antisense oligonucleotides capable of binding to multiple targets and their use in treatment of respiratory disease)

RN 186470-22-4 CAPLUS

CN DNA, d(P-thio)(G-T-G-G-G-C-C-T-A-G-C-T-C-T-C-G-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS

IT 186470-22-4P

RL: PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of treatment for lung diseases using antisense oligonucleotides)

RN 186470-22-4 CAPLUS

CN DNA, d(P-thio)(G-T-G-G-G-C-C-T-A-G-C-T-C-T-C-G-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS

IT 186470-22-4P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(antisense oligonucleotides directed against adenosine A1 or A3 receptors for treatment of asthma)

RN 186470-22-4 CAPLUS

CN DNA, d(P-thio)(G-T-G-G-G-C-C-T-A-G-C-T-C-T-C-G-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d ibib abs 1-3

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1999:219995 CAPLUS

DOCUMENT NUMBER: 130:306599

TITLE: Antisense oligonucleotides capable of binding to multiple targets and their use in the treatment of respiratory disease

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913886	A1	19990325	WO 1998-US19419	19980917
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9893951 A1 19990405 AU 1998-93951 19980917
 PRIORITY APPLN. INFO.: US 1997-59160 19970917
 US 1998-93972 19980609
 WO 1998-US19419 19980917

AB Antisense oligonucleotides carrying sequences that will allow them to bind

to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single treatment for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.ltoreq.15%) and may have adenosines substituted with analogs. These oligonucleotides are targeted to high (G+C) sequences within mRNAs.

Thus,

phosphorothioate antisense oligonucleotide (HAdAlAS, 5'-gatggagggcgccatggcggg-3') designed for the adenosine A1 receptor is provided. HAdAlAS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house

dust

mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition assocd. with lung airway, such as bronchoconstriction, inflammation, or allergies.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:145207 CAPLUS

DOCUMENT NUMBER: 126:148487

TITLE: Method of treatment for lung diseases using antisense oligonucleotides

INVENTOR(S): Nyce, Jonathan W.; Metzger, W. James

PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.; Metzger, W. James

SOURCE: PCT Int. Appl., 71PP

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640162	A1	19961219	WO 1996-US9306	19960606
W: AL, AM, AT, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5994315	A	19991130	US 1995-474497	19950607
CA 2223776	AA	19961219	CA 1996-2223776	19960606
AU 9660959	A1	19961230	AU 1996-60959	19960606
EP 831848	A1	19980401	EP 1996-918260	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192686	A	19980909	CN 1996-196115	19960606

JP 11507218 T2 19990629 JP 1996-501658 19960606
 PRIORITY APPLN. INFO.: US 1995-474497 19950607
 WO 1996-US9306 19960606

AB A method of treating airway disease in a subject in need of such treatment is disclosed. The method comprises topically administering to the subject an antisense oligonucleotide in an amt. effective to treat the airway disease, where the antisense oligonucleotide is essentially free of adenosine. Pharmaceutical formulations are also disclosed.

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS
 ACCESSION NUMBER: 1997:130067 CAPLUS
 DOCUMENT NUMBER: 126:135600
 TITLE: Antisense oligonucleotides directed against adenosine A1 or A3 receptors for treatment of asthma
 INVENTOR(S): Nyce, Jonathan W.
 PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.
 SOURCE: PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640266	A1	19961219	WO 1996-US8325	19960603
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2223769	AA	19961219	CA 1996-2223769	19960603
AU 9660295	A1	19961230	AU 1996-60295	19960603
AU 699330	B2	19981203		
EP 831924	A1	19980401	EP 1996-917910	19960603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1192158	A	19980902	CN 1996-195955	19960603
AU 9918574	A1	19990506	AU 1999-18574	19990303
PRIORITY APPLN. INFO.: US 1995-472527 19950607				
AU 1996-60295 19960603				
WO 1996-US8325 19960603				

AB A method of reducing bronchoconstriction in a subject in need of such treatment is disclosed. The method comprises administering to the subject an antisense oligonucleotide mol. directed against the A1 or A3 adenosine receptor in an amt. effective to reduce bronchoconstriction. The method is useful for treating patients afflicted with asthma. Pharmaceutical formulations are also disclosed.

=> s ggcggcctggaaagctgagatggagggcgccatggcgggcacaggctgggc/sqsn

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...
 Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L8 2 L7

=> d fhitr ibib abs 1-2

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1999 ACS

IT 208884-01-9

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human adenosine A1 receptor-specific; antisense oligonucleotides
capable of binding to multiple targets and their use in treatment of
respiratory disease)

RN 208884-01-9 CAPLUS

CN DNA (synthetic human adenosine A1 receptor mRNA-binding cDNA) (9CI) (CA
INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1999:219995 CAPLUS

DOCUMENT NUMBER: 130:306599

TITLE: Antisense oligonucleotides capable of binding to
multiple targets and their use in the treatment of
respiratory disease

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913886	A1	19990325	WO 1998-US19419	19980917
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9893951	A1	19990405	AU 1998-93951	19980917
PRIORITY APPLN. INFO.:			US 1997-59160	19970917
			US 1998-93972	19980609
			WO 1998-US19419	19980917

AB Antisense oligonucleotides carrying sequences that will allow them to bind

to more than one mRNA in a target cell are described. Such oligonucleotides can be used as a single treatment for diseases having more than one contributing pathway. In particular, oligonucleotides effective against genes involved in the etiol. of respiratory disease are targeted. Preferably, the oligonucleotides are low in adenosine (.1 to req. 15%) and may have adenosines substituted with analogs. These

oligonucleotides are targeted to high (G+C) sequences within mRNAs.

Thus, phosphorothioate antisense oligonucleotide (HAdAlAS, 5'-gatggagggcggcatggcggg-3') designed for the adenosine A1 receptor is provided. HAdAlAS significantly and specifically reduces the in vivo response to adenosine challenge in a dose-dependent manner, is effective in protection against aeroallergen-induced bronchoconstriction (house dust mite), has an unexpected long-term duration of effect (8.3 days for both PC50 adenosine and resistance), and is free of side effects that might be toxic to the recipient. Such oligonucleotides may be used for treating a disease or condition assocd. with lung airway, such as bronchoconstriction, inflammation, or allergies.

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1999 ACS

IT 208884-01-9

RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nucleotide sequence; antisense oligonucleotides for treatment of respiratory ailments and lung inflammation)

RN 208884-01-9 CAPLUS

CN DNA (synthetic human adenosine A1 receptor mRNA-binding cDNA) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE

ACCESSION NUMBER: 1998:385522 CAPLUS

DOCUMENT NUMBER: 129:72195

TITLE: Agent and method of treatment for diseases and conditions associated with respiratory ailments and lung inflammation

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA; Nyce, Jonathan W.

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9823294	A1	19980604	WO 1997-US22017	19971126
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9853688	A1	19980622	AU 1998-53688	19971126
EP 946201	A1	19991006	EP 1997-950775	19971126
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRIORITY APPLN. INFO.:			US 1996-757024	19961126
			WO 1997-US22017	19971126

AB An agent comprises anti-sense oligos directed to adenosine receptors for alleviation of respiratory ailments and inflammation. The agent is provided as a compn., various formulations, and kit. The present agents